Overview of Human Health and Chemical Mixtures: Problems Facing Developing Countries

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In developing countries, chemical mixtures within the vicinity of small-scale enterprises, smelters, mines, agricultural areas, toxic waste disposal sites, etc., often present a health hazard to the populations within those vicinities. Therefore, in these countries, there is a need to study the toxicological effects of mixtures of metals, pesticides, and organic compounds. However, the study of mixtures containing substances such as DDT (dichlorodiphenyltrichloroethane, an insecticide banned in developed nations), and mixtures containing contaminants such as fluoride (of concern only in developing countries) merit special attention. Although the studies may have to take into account simultaneous exposures to metals and organic compounds, there is also a need to consider the interaction between chemicals and other specific factors such as nutritional conditions, alcoholism, smoking, infectious diseases, and ethnicity. *Key words:* chemical mixtures, developing countries, hazardous waste, heavy metals, pesticides. *Environ Health Perspect* 110(suppl 6):901–909 (2002). *http://ehpnet1.niehs.nih.gov/docs/2002/suppl-6/901-909yanez/abstract.html*

Many of the environmental issues in industrial countries are of little concern to developing nations, where morbidity from infectious diseases is high and programs for economic development to provide a minimum quality of life are the first priority (*1*). Therefore, health policies are most often designed to have immediate impact, and they usually and rightly concentrate on the control of communicable diseases (*1,2*).

Taking this issue into account, the appearance of hazardous sites in less developed nations because of the lack of waste management programs is understandable (*2–4*). These sites are evidently becoming an important source of complex mixtures (*5*). However, industrial areas, small-scale enterprises, the production and use of pesticides, mining activities, and even atmospheric pollution are other important sources of toxic mixtures (*4–8*). Several international organizations such as the Pan-American Health Organization (*6*) and the Association of Southeast Asian Nations (*7*) are studying the contaminants of concern to their respective regions, including arsenic, cadmium, lead, mercury, and several pesticides and solvents. This list might not be different from that of any developed country. Yet, considering that some developing nations currently use substances such as the insecticide DDT (dichlorodiphenyltrichloroethane) and have particular contaminants such as fluoride, it becomes evident that the chemical mixtures in these nations are significantly different. This article is a brief review of health issues related to mixtures of metals, pesticides, and hazardous wastes in developing countries.

Metals

Pyrometallurgic nonferrous metal production is the major global source of airborne arsenic, cadmium, copper, zinc, and lead (*9*). The metallurgics are also primary sources of cadmium, nickel, and lead in aquatic ecosystems (*9*). In soil, the most important sources of metals worldwide are mine tailings, smelter wastes, and atmospheric fallout (*9*). Several of these sources are located in developing countries. For example, Tunisia and Lebanon are major contributors of lead, nickel, and cadmium to the atmosphere of the Mediterranean region (*10*).

Smelters. About 60% of the smelters of the world are located in developing nations (*11*); China alone has 116 aluminum smelters, 50 copper smelters, and 770 lead–zinc smelters (*12*). Taking into account that different metals are emitted by these industries (*13,14*), they have to be considered important sources of metal mixtures. In fact, metal mixtures around smelters have been observed in different environmental media (Table 1 gives some examples).

In this scenario biota and humans are exposed to metal mixtures (*15,16,20,21*). For example, in the smelter town of Torreon in Mexico (*21*), in the area closest to the lead smelter, 77% of the studied children had lead levels higher than 20 µg/dL [reference guideline: 10 µg/dL (*22*)], with a median arsenic concentration in urine of 123.9 µg/L [reference guideline: 50 µg/g creatinine (*23*)]. Furthermore, health effects such as cancer (*24*) and neuropsychological disorders (*25*) have also been reported around smelters. Given these observations, it is interesting to note that experiments have found some alterations in central monoaminergic systems in animals treated with the mixture of lead plus arsenic (*26*).

Considering chemical mixtures, it is important to point out that smelters release not only metals but also sulfur dioxide (*27*) and air particles (*28,29*). The presence of different metals in particles has been noted around a copper smelter in Mexico (*29*): all the arsenic, 86% of the copper, and 71% of the lead were concentrated in particles < 2.0 µm, whereas the zinc was located in particles > 2.0 µm (*29*). The relevance of these data to health issues is demonstrated in Chile, where respiratory problems related to the simultaneous exposure to sulfur dioxide and air particles were found in children (*30*).

In developing nations, secondary smelters deserve special attention because they are also an important source of metals. For example, in a rural community of Bolivia, where three secondary smelters operated, arsenic and lead contents in soil and household dust were found at levels above international guidelines, exposing children living in this community to those metals (*31*). Further evidence that secondary smelters are a source of metal mixtures comes from a report produced in Mexico: women living around these smelters had higher levels of arsenic, cadmium, and lead in placental tissue than women from a nonindustrial community (*32*).

These types of smelters have been related to more than just metal mixtures. Mixtures of metals and dioxins warrant more studies. For example, battery recycling is an important source of lead in developing countries. This is demonstrated by cases such as workers in India (*33*) and children living in Trinidad and Tobago, whose blood lead levels averaged 72.1 µg/dL in a locality contaminated by wastes from such battery recycling (*34*). At the same time, it has been reported that secondary nonferrous metal smelters such as aluminum, copper, and lead smelters are important sources of dioxins (*35*).

Mining. The *London Mining Journal*'s 1999 annual review detailed 158 countries for which mining is a significant contributor to

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the national economy (*36*). A high proportion of minerals have in fact been mined in developing countries for many years (*36*). In China alone, the mining industry is enormous, including 8,523 iron ore mines, 2,003 copper mines, and 3,323 lead–zinc mines (*12*). Therefore, mining in less developed nations is also responsible for significant productions of arsenic, cadmium, lead, mercury, and fluorspar (*37*). For instance, less developed nations produce almost 50% of the world's lead (*38*).

Another big problem of the mining industry is waste management. Consider that 1,000 tonnes of ore, at an average grade of 0.91%, will result in 9 tonnes of metal and 990 tonnes of waste (*36*). This presents an enormous problem considering that the estimated world production of metals in 1999 was around 1 billion tonnes (*36*). The combined wastes generated by extraction and milling are known as tailings. Tailings contain complex mixtures of metals, which are transported to surrounding communities by air, soil, and water contamination (*36*). In the Philippines, mining companies dispose of more than 35,000 tonnes of tailings per day, resulting in damage to agricultural lands and irrigation systems (*7*); and in the Slovak Republic, monitoring programs in two different mines have detected 19 elements derived from mine waters and mine tailings that are entering the environment (streams, sediments, etc.) at different levels (*39*). In the surroundings of mining sites, metal mixtures can be found at very high levels, as demonstrated by the levels of four metals in soil and sediments around a Mexican mining site presented in Table 2.

Table 1. Examples of environmental contamination around smelter sites.

Country	Matrix	Metals	Reference
Croatia	Soil (ppm)	Pb - 1,420 Cd - 11 Zn - 335	(*15*)
Mexico[a]	Soil (ppm)	Pb - 1,185 Cd - 47 As - 1,396	(*16,17*)
Mexico[a]	Air (µg/m^3)	Pb - 1.9 Cd - 0.1 As - 1.4	(*16,17*)
Mexico[b]	Street dust (ppm)	Pb - 2,448 Cd -112 As - 113	(*19*)
Brazil	Water (ppb)	Mn - 697 Cd - 13	(*18*)
Brazil	Sediments (ppm)	Mn - 32,276 Ni -170 Cr - 174	(*18*)

Canadian Environmental Quality Guidelines (*154*) are as follows—Residential soil: lead, 70 ppm; cadmium, 10 ppm; zinc, 200 ppm; arsenic, 12 ppm. Water: manganese, <50 ppb; cadmium, 5 ppb. Sediments: chromium, 37.3 ppm. [a]Copper smelter in San Luis Potosí. [b]Lead smelter in Torreon.

Therefore, environmental contamination in mining sites may be considered a public health issue because millions of people are exposed to metals from these sites. Considering that miners represent approximately 1% of the global workforce, or about 30 million workers (*41*), and using numbers obtained in Mexican mining towns of 10 individuals who were not miners per mining worker, it can be estimated that 300 million people may be exposed to metal mixtures in mining towns worldwide. However, the number of individuals exposed to metals because of mining activities might be larger if we consider the potential distribution of these elements in the environment. Human exposure to metals has been described at mining sites (*42–44*); however, studies of people exposed to metal mixtures at those sites are not easily found in the literature. At a mining site in Mexico (the same site described in Table 2), we have found that 31% of the studied children had lead levels in blood higher than 10 µg/dL, and 71% had urinary arsenic concentrations higher than 50 µg/creatinine (*45,46*). In those children, an increased frequency of apoptosis has been found in blood cells (*47*).

Small-scale mining. The International Labour Organization reported that small-scale mining activity grew by an average of 20% in the last 5 years in 35 countries in Africa, Asia, and Latin America (*48*). An estimated 13 million people are engaged in small-scale mining, including about 4 million women and hundreds of thousands of children (*48*). Moreover, an even larger number of people, between 80 million and 100 million, may depend on small-scale mining for their livelihood (*48*). This type of mining includes copper, iron ore, lead, zinc, manganese, nickel, coal, and gold.

Although traditional mining operations are important sources of metals, mercury contamination associated with small-scale gold mining and processing presents a major hazard for the environment and humans in at least 25 countries from Latin America, Asia, and Africa (*49–52*). The 4,500-year-old tradition of using amalgamation as a mining process continues to be practiced. Spanish colonizers used mercury for gold recovery, and it is estimated that between the years 1550 and 1880, nearly 200,000 tonnes of mercury were released to the environment (*49*). With the process of amalgamation, the gold present in the ore is extracted by adding liquid mercury, forming gold amalgam. To separate the gold from the mercury, the amalgam is simply heated in the open by blow torches (*53*). Gravimetric material flow analyses show that 70–80% of the mercury is lost to the atmosphere during processing, and 20–30% of it goes into tailings, soils, stream sediments, and water (*51*). For every gram of gold, 1.2–1.5 g of mercury is lost to the environment (*51*). Several studies have demonstrated mercury contamination in the ecosystems as a result of gold mining (*49,54–56*).

Table 2. Environmental contamination around a mining site in San Luis Potosi, Mexico [ppm (mg/kg)].

Matrix	Arsenic	Lead	Zinc	Copper
Sediments	28,600	2,010	5,940	978
Surface soil	17,400	3,450	6,270	7,200

Data from Razo et al. (*40*). Canadian Environmental Quality Guidelines (*154*) are as follows—Residential soil: lead, 70 ppm; copper, 63 ppm; zinc, 200 ppm; arsenic, 12 ppm. Sediments: arsenic, 5.9 ppm; lead, 35 ppm; zinc, 123 ppm; copper, 35.7 ppm.

However, regarding mixtures, two issues deserve further attention. First is the mixture of the mercury species. In the Amazonian Basin, for example, populations who are exposed to methylmercury through fish consumption may also be exposed to the elemental mercury used in the amalgamation of gold (*57*). The second issue involves individuals who may be simultaneously exposed to other metals. Such is the case in Tanzania, where high levels of arsenic, lead, and mercury were quantified in tailings (*51*); and in Ecuador, where artisanal gold mining has resulted in extensive contamination of the fluvial environment by different metals (*58*). In Ecuador, mercury, arsenic, cadmium, and copper in many sediment samples from two areas exceed the Environment Canada Sediment Quality Toxic Effect Threshold for the Protection of Aquatic Life by factors of 10 to >1,000 (*58*). Studies of humans exposed to mixtures are needed in small-scale mining areas because many investigations have been limited to the study of human exposure to mercury (*49,56*). Furthermore, taking into account that many of the artisanal mining areas are located in malaria zones, and considering that, worldwide, DDT was used until recently for the control of malaria, it would be interesting to study co-exposure to DDT and mercury because they share similar properties. For example, both are persistent, both bioaccumulate, and both are neurotoxic and genotoxic agents (*59,60*). In this regard, neurotoxic (*61*) and cytogenetic damage (*62*) have been reported in individuals exposed to mercury in the gold mining areas.

Natural sources. High levels of fluoride in water sources have been identified in at least 25 countries, 23 of which are developing nations such as Mexico, Argentina, China, India, Pakistan, Bangladesh, Uganda, Kenya, and Tanzania (*63*). In Mexico, around 5 million inhabitants live in areas with fluoride levels higher than the 1.5 mg/L national guideline (*64*), whereas in India, 62 million people, including 6 million children, are exposed to fluoride (*65*).

High levels of arsenic, another pollutant of natural waters, have been found in 10 developing countries, including Taiwan, China, India, Bangladesh, Mexico, Argentina, Chile, and Romania (*66,67*). In these countries, approximately 45 million individuals are exposed to arsenic by drinking water (*66,67*). In Bangladesh, 57.5% of the studied population had skin lesions caused by arsenic poisoning (n = 1,630 adults) (*68*).

Comparing the lists of the countries whose inhabitants are exposed to fluoride with those whose populations are exposed to arsenic shows that nations such as Mexico, Argentina, China, Bangladesh, and India are on both lists. In fact the presence of arsenic and fluoride in the same aquifers has already been found in Mexico (*69–71*). Moreover, a positive correlation was found between the urinary concentrations of these elements in exposed children (*72*). In humans, the absorption rate, the proportion of urinary excretion, and the biological half-life did not show statistically significant differences between drinking water containing high arsenic alone and drinking water containing varied high levels of arsenic and fluoride. Similar results were observed for fluoride (*73*). However, it is important to study the toxicologic interaction of both elements in soft tissues, especially because contradictory results have been found in China in individuals and animals simultaneously exposed to arsenic and fluoride (*73*). These elements may have some mechanisms of toxicity in common. For example, arsenic increases oxidative damage (*74,75*), and fluoride effects are reduced by free radical scavengers (*76*).

Metals of concern. Considering all these data, arsenic, lead, cadmium, mercury, fluoride, and manganese may be listed as some of the metals of concern for developing countries. Because of this, it is important to study the toxicological interactions between them. For example, we have shown that cadmium increases the toxicity of arsenic in rats (*77,78*), whereas in mice, the mixture of arsenic and lead provoked a 38% decrease of norepinephrine in the hippocampus and a 90% increase of serotonin in the frontal cortex (*26*). These types of studies are important for the risk assessment of metal mixtures in human populations.

Pesticides

Presently, approximately 1,500 active ingredients have been registered as pesticides (*79*). Formulators mix these compounds with one or more of some 900 "inert" ingredients to create approximately 50,000 commercial pesticides registered for use (*79*). Because of the enormous number of commercial formulations, pesticides are available to almost every community. For example, in a study conducted in Kenya, researchers identified 21 pesticides used by small-scale farmers (*80*); in China, the number of registered pesticide formulations was about 1,600 in 1996 (*81*).

Pesticides are used for a wide variety of applications in different fields. Roughly 85% of the pesticides currently used in the world are devoted to the agricultural sector, almost 10% are dedicated to sanitary measures against vectors in public health programs, and the rest are applied in specific sites such as buildings, transport media, and residential areas (*79*). Pesticides can be divided into different classes according to their function. Almost every country makes general use of all the major pesticides, but they each use specific sets of pesticides in correspondence with their typical crop. For example, herbicides account for 75% of the total pesticide use in Malaysia, followed by insecticides, which account for 13%. In contrast, in the Philippines, insecticides are 55% of the market, followed by fungicides at 20% (*7*). In India, where the demand for pesticides in terms of value is about 2% of the total world market, 76% of the pesticides used are insecticides (*82*). In Latin America, during the 1980s, herbicides were the major type of pesticides used in the region, but again, each country has its own preferences. For example, in Colombia, fungicides have the major percentage of the market (*83*).

An important difference between countries, however, is that pesticides banned in developed countries continue to be in use in developing ones. Among these banned pesticides are three herbicides (butachlor, haloxifop, and nuarimol) and two insecticides (prothiophos and DDT) (*79*). To illustrate the gravity of the situation, it is important to note that in 1995–1996, 21 million pounds of pesticides prohibited in the United States were exported from U.S. ports (*84*). Most of these were shipped to developing countries (*84*). Furthermore, many older, nonpatented, more toxic, environmentally persistent, and inexpensive chemicals are used extensively in developing countries, thus creating serious acute health problems and local as well as global environmental contamination (*85*). In other words, pesticides play a big role in the chemicalization of developing countries (*86*).

The sale of pesticides is in fact higher in developed countries; however, pesticide-related poisonings are far more frequent in less developed countries (*83*). Estimates made by the World Health Organization (WHO) indicate that three million acute poisonings may occur annually in the world (*79*). It has also been estimated that 99% of the deaths related to pesticide poisonings occur in developing regions (*83*). In Latin America, 12–13% of the workers have been intoxicated with pesticides at least once (*83*). It is important to make this distinction because other estimations, also provided by WHO, show that two-thirds of the 3 million global acute poisonings are indeed related to intentional intoxications (*79*). In some countries pesticides have become the most popular method of self-harm (*87*).

Three key factors may explain the high prevalence of poisonings in the less developed nations: *a*) the kind of pesticides that are being used in these countries, for example, in Brazil, where 60% of the pesticides fall in the highly or moderately toxic classes (*79,85*); *b*) the lack of knowledge and improper practices on the part of handlers (*85,88*); and *c*) the poor-quality formulations used in these nations. WHO and the Food and Agriculture Organization warned, in a joint statement, that approximately 30% of pesticides marketed in developing countries do not meet internationally accepted quality standards (*89*). These pesticides frequently contain hazardous substances and impurities that have been banned or severely restricted elsewhere (*89*). For example, many formulations contain the active ingredient in concentrations outside internationally accepted tolerance limits (*89*).

Although these factors may explain the number of intoxications, researchers have become increasingly aware of underreporting. The actual numbers may be even higher than those recognized by different organizations (*86*). Health assessments are urgently needed for the study of nonoccupational exposures because most of the studies performed in developing nations focused only on workers. This is understandable if we consider that an estimated 1.3 billion workers are active in agricultural production worldwide, and almost 60% of them are in developing countries (*90*). However, WHO estimates that 5% of the total population in agricultural regions lives in areas heavily exposed to pesticides (*83*). In Latin America alone this percentage represents almost 6 million persons nonoccupationally exposed to pesticides.

Therefore, it is evident that further assessments of the health risks of pesticides to humans are needed, but these assessments may encounter significant limitations. In general the assessments of toxicological risks in experimental models are performed using single compounds; however, in practice, agricultural workers and communities living near agricultural fields are commonly exposed to formulations and mixtures of pesticides. For example, in a rural community of Mexico, nine insecticides and five herbicides are being used only for sugar cane. The commercial formulation is a mixture in itself, having an active ingredient and one or more inert ingredients—that serve as a vehicle for the toxins. In general the toxicity of these vehicles is rarely considered, although they alone constitute a large part of commercial production and have adverse effects that occasionally exceed those of the active ingredients. For example, carbon tetrachloride and chloroform can be used as inert ingredients without being mentioned in the label (*79*).

To further understand the effects of chemical mixtures in developing countries, investigators must examine the particular toxicity of the insecticides found in each country. For example, it has generally been assumed that the lower toxicity of pyrethroids combined with their slow skin penetration make them safer (*91*). Consequently, in developing countries such as Brazil, Mexico, and others in Central America, pyrethroids are becoming popular (*92*). However, as a result of aberrant agricultural practices, permethrin (PM) is being used in combination with methyl parathion (MP). We have previously shown that when a commercial formulation of MP was administered to rats at 464 mg/kg, the LD_{50} of a commercial formulation of PM was reduced by 37% ($p < 0.001$) (*93*). Furthermore, PM decreased the MP-induced inhibition of the cholinesterase activity. With MP, an inhibition of about 90% of the activity of the enzyme was found at a nonlethal dose, whereas in rats treated with any type of mixture containing MP + PM, the inhibition was only around 40% ($p < 0.05$). The results indicate that a commercial formulation containing MP increases the acute toxicity of a commercially formulated product of PM, whereas the latter decreases the MP-induced inhibition of brain cholinesterase activity.

Interactions between pesticides can be expected, either because they have common cellular targets (*94*) or because they have common metabolic pathways. The effect of MP on the toxicity of PM can be explained by an inhibition of the carboxylesterase involved in the main metabolic pathway of PM (*95–97*). Organophosphates, including malathion and parathion, inhibit the activity of this enzyme (*96–98*). It is possible that in rats treated with both formulations, the inhibition of the carboxylesterase activity may increase the concentration of PM, thus yielding greater toxicity. In humans, an interaction between pyrethroids and organophosphates has been reported (*99*). Furthermore, in China, the prevalence of acute poisoning in farmers with exposure to combined insecticides and single organophosphate insecticides was 10.1% and 2.3%, respectively (*81*), and the number of cases of acute poisoning caused by exposure to organophosphate–pyrethroid mixtures reported in Chinese medical journals in the late 1990s was about 4 times greater than the number reported in the late 1980s (*81*).

Given this information, it is clear that more exposure assessments are needed in high-risk populations. Biomarkers of exposure have been described for the majority of the pesticides (*100*). Therefore, they may be useful for identification of high-risk groups such as those in developing countries, where undesired health effects (e.g., cancer, neurobehavioral effects, reproductive dysfunctions, etc.) may arise not only as a consequence of acute intoxication but also as a result of low-dose, long-term exposure (*101*). Studies in areas with endemic malaria may help to illustrate this issue.

Malaria causes at least 300 million cases of acute illness each year (*102*) but exerts its heaviest toll in Africa, where approximately 90% of the more than 1 million deaths from malaria worldwide occur each year. DDT has been used in the control program for malaria since 1955, and at the peak of the campaign, 70,000 tonnes of the insecticide were applied each year in 100 million dwellings worldwide (*103*). Houses were sprayed twice a year with DDT to control the spread of this disease. Today, DDT has been replaced in many countries with agents such as pyrethroids. Therefore, in many malaria areas in the developing world, individuals, particularly children, are now simultaneously exposed to residual DDT and to pyrethroids, as was shown in malaria areas in Mexico (*104*).

In conclusion, the study of mixtures of commercial formulations is needed in developing countries. This is further supported by taking into account *a*) the large number of mixtures in the market and *b*) the differences in the formulations across countries. The example of China illustrates the first point, as more than 600 kinds of pesticide mixture preparations, mainly containing organophosphorous insecticides, have been produced and applied in that country in recent years (*81*). The second point is illustrated by specific countries that have different formulations of the same insecticide. For example, we have learned that in some developed nations xylene is not present in the commercial formulation of PM, whereas in Mexico xylene used to be the main ingredient in some formulations of this insecticide. In addition the case of Pakistan demonstrates the risks associated with some formulations: During 1976, an epidemic of malathion poisonings affected 40% of applicators and mixers employed in the malaria control program in Pakistan. When the epidemic was over, 2,800 subjects had experienced at least one episode of acute poisoning (*101*). Three different malathion commercial formulations had been used, all containing the same concentration of malathion but varying in the content of the contaminant isomalathion. Laboratory analyses showed that the intensity of acute toxicity was determined by the content of isomalathion (*101*).

The use of pesticides worldwide has increased from 1.5 million tonnes in 1970 to 3.0 million in 1985 (*79*). An increase of 280% has been estimated just for Latin America between 1980 and 2000 (*83*). Therefore, it is essential that a national plan for the prevention of pesticide risk be established in every country. Protection of the community and the workers exposed to pesticides must be a fundamental mandate for governments and public health officers around the world (*101*).

Hazardous Waste

The output of hazardous wastes worldwide was about 400 million tonnes a year in the early 1990s. Of these, some 300 million tonnes were produced by countries that are members of the Organisation for Economic Co-operation and Development (*105*), mainly from chemical production, energy production, pulp and paper factories, mining industries, and leather and tanning processes. Furthermore, in the majority of low-income countries, health care waste is usually not separated into hazardous or nonhazardous waste. In these countries the total health care waste per person per year is anywhere from 0.5 kg to 3 kg (*106*).

In less developed nations, environmental problems connected to improper disposal of hazardous wastes are increasing, and in some communities they have become an issue of public health. For example, in the Czech Republic and in Slovakia, approximately 670,000 hectares of land have been contaminated by toxic waste (*8*). In Hungary no capacity exists for about two-thirds of the hazardous waste that would need special treatment; furthermore, severe problems may emerge because more than 10,000 abandoned disposal sites are dispersed all over the country (*4*). In Latin America (*107*) and Southeast Asia (*7*), problems are similar to those found in Eastern Europe (*4,8,108*). In developing countries, additional hazards occur from scavenging on waste disposal sites and manual sorting of the waste recovered at the back doors of health care establishments (*107*). These practices are common in many regions of the world.

In Mexico almost 90% of the hazardous waste is managed with inadequate control (*109*). However, information about the locations where the waste is being disposed is scanty (*110*). Therefore, our group designed a method for locating of these sites (*111*). Preliminary results from the State of San Luis Potosí show that in this Mexican state alone, 47 sites are potentially contaminated with hazardous wastes (*2,5*). Considering that Mexico has 32 states, the magnitude of the problem can be clearly recognized. Of the 47 sites listed for San Luis Potosí, 60% have problems with organic compounds (including pesticides) and 53% have problems with metals. More than one contaminant of concern has been identified at almost all of these sites.

The case of Guadalcazar may be a good example to illustrate the health hazards associated with exposure to chemical mixtures coming from a toxic waste disposal site. Guadalcazar is located in the central region of Mexico. During 8 months of operation, the site received 14,000 tonnes of hazardous waste of industrial origin. We calculated that 9,390 tonnes of waste contained lead, 6,840 tonnes contained chromium, 1,348 tonnes contained mercury, 53 tonnes contained nickel, 52 tonnes contained arsenic, and 32 tonnes contained asbestos. For organic compounds, data were even more scarce: 4,758 tonnes were oils or solvents, but in some of the samples organochloride compounds were found (*112*). The waste was deposited in drums and bulk material. Thus, workers at the site were exposed to the toxics through several pathways. Compared with a control population, the exposed workers exhibited significantly higher frequencies of chromatid and chromosomal deletions, the magnitude of which was related to exposure time (*113*).

Another issue important for developing nations is the international traffic of hazardous wastes. Progressively tighter regulatory control measures have increased the costs of waste disposal in many countries. Exporting this waste to developing countries, which are regulated by less stringent measures and have lower public awareness of the issue, has been one way in which some companies have evaded these tighter regulations. Officially, fewer than 1,000 tonnes of waste a year are traded to developing countries. However, the illegal traffic of hazardous waste poses a serious threat to the environment and to human health (*105*). The following example serves to illustrate this problem.

In December 1998, 2,700 tonnes of industrial waste containing high levels of mercury and other metals, possibly in addition to other toxic compounds, were shipped illegally to Sihanoukville, Cambodia. Once there, the waste was unloaded and transferred to a nearby inland dumpsite. An estimated 2,000 Sihanoukville residents were exposed to the waste occupationally or environmentally, and at least six deaths and hundreds of injuries have been associated with the incident (*114*).

Another emerging issue regarding hazardous waste is electronic waste. Referred to as E-waste, it is the most rapidly growing waste problem in the world. European studies estimate that the volume of E-waste is increasing by 3–5% per year, which is almost 3 times faster than the general growth of the municipal waste stream (*115*). The average life span of a computer has shrunk from 5 years to 2 years (*116*). In 1998 it was estimated that 20 million computers became obsolete in the United States alone, and the overall E-waste was estimated to be anywhere from 5 to 7 million tonnes (*116*). A great amount of the E-waste from industrial countries is exported to developing ones such as China, Pakistan, and India (*115*). In these countries the E-waste is recycled by individuals without any protection. This activity represents a health hazard because E-waste contains lead and cadmium in monitor cathode ray tubes and circuit boards, mercury in switches and flat screen monitors, cadmium in computer batteries, polychlorinated biphenyls in older capacitors and transformers, and brominated flame retardants on printed circuit boards, plastic casings, and cables (*115*). Other chemicals that can be found in E-wastes are polyvinyl chloride (PVC; dioxins can be formed when PVC is burned), chromium, barium, beryllium, and carbon black, the main ingredient in toner (*115*). Millions may be exposed to these chemicals; for example, the total number of workers employed in just one Chinese city where occidental E-waste is recycled has been estimated to be 100,000 (*115*). Sediment samples collected near this city showed barium, copper, lead, nickel, zinc, chromium, and cadmium at levels far above the guidelines of the U.S. Environmental Protection Agency (U.S. EPA) (*115*). Although transboundary movement of E-waste is an issue that deserves special attention, to have a complete picture of the problem we have to consider that developing countries also generate E-waste. For example, an estimated 300,000 scrap personal computers are generated each year in Taiwan (*117*).

Developing countries are not using the appropriate technology for waste management. Therefore, health risk assessments are required for the analysis of hazardous waste sites. The studies may need to consider the simultaneous exposure to metals and organic compounds, thus making experimental models necessary for the study of the toxicological interactions among such contaminants.

Food

Food is another source of chemical mixtures. Therefore, it is important to take into account the differences among regional diets. For example, the diet of the average European person contains almost twice the total grams of food per day compared with that of the average African or East Asian person (*118*). Furthermore, the average European eats double the amount of vegetables consumed by the average person in East Asia and Latin America, and 5 times the amount consumed in by persons in Africa (*118*). Differences also exist in specific items. For example, cassava is not consumed in the European diet but is an important food item in Africa and in Latin America (*118*). Cassava is a low-protein, starchy staple that has one disadvantage: the fleshy roots contain poisonous compounds that must be removed (cyanogenic glycosides—compounds that liberate cyanide). In Africa alone cassava is consumed at a rate of about 63 million tonnes a year (*119*). Regarding organic pollutants, it is essential to consider that the proportion of milk and milk products is less significant in the diet of developing nations (*118*) and that the consumption of marine fish in developing countries is 2–9 times higher than in developed ones (*118*). Organochlorine pesticides have been found in milk products and vegetables in India and in fish from Southeast Asian countries (*120*).

Indeed, foodborne exposure to agricultural and environmental chemicals concerns public health officials in most countries. The little published information available in developing countries indicates that the general population is exposed to a mixture of pesticide residues in food. For example, in Kuwait (*121*) and in Thailand (*122*) numerous pesticides were found in different food items. Although the majority of them were within the established acceptable daily intake levels, there is a need to acknowledge the effects of the mixture. Among 24 pesticides encountered throughout an 8-year study in Thailand, such toxic pesticides as DDT, dimethoate, methamidophos, and MP were found every year (*122*).

Finally, in many countries, food represents the pathway through which children are exposed not only to chemical contaminants but also to biological ones. For example, approximately 1,500 million global episodes of diarrhea occur annually, resulting in the deaths of 3 million children younger than 5 years (mainly in developing countries) (*123*). It is estimated that 70% of these annual cases of diarrhea worldwide have been caused by biologically contaminated food (*123*). Foodborne parasitic diseases also present a major public health problem. For example, foodborne trematodes affect 40 million people, with more than 10% of the world's population at risk of infection (*123*). The adverse health effects of the interactions between chemical and biological contaminants remain to be determined.

Air Pollution

This topic is a complex one, and a complete review of it is out of the scope of the present work. However, a few examples will illustrate the health risks associated with air pollution in less developed countries.

A causal relationship between ambient air pollution and daily mortality and morbidity rates has been reported in different studies (*124,125*). The relevant contaminants involved make the mixture effect clearly evident, including sulfur dioxide, suspended particulate matter, nitrogen dioxide, carbon monoxide, ozone, and lead (*124*). Furthermore, ambient air pollution has been declared a relevant health problem, particularly regarding developing countries. A considerable burden of disease has been reported for such cities as New Delhi, India (*126*); Santiago, Chile (*127*); and Mexico City, Mexico (*128*). In 22 developing countries, the World Resources Institute found that 180 cities had air quality that did not achieve the WHO guidelines (*129*). In these cities alone, around 360 million people are exposed to mixtures of air pollutants (*129*). Furthermore, considering that the urban population in developing nations is expected to increase from 1.94 billion to 3.88 billion in the next 30 years (*130*), we can expect air pollution in urban areas to remain a significant problem.

It is also important to address the particular problems that rural communities in developing countries face regarding air pollution. First, it is estimated that 70% of the poorest people in developing countries live in rural areas (*130*). In addition to this, approximately 50% of the world's population and up to 90% of rural households in developing countries still rely on coal or unprocessed biomass material in the form of wood, dung, and crop residues, for fuel (*131*). Therefore, although ambient air pollution is an important source of chemical mixtures, it is evident that in developing countries indoor air pollution poses a greater threat.

High levels of indoor air pollutants result from the use of either open fire or poorly functioning stoves to burn biomass or coal. Women, especially those responsible for cooking, are therefore the ones most heavily exposed, along with their children (*131*). Many of the substances in smoke from either biomass or coal can be hazardous to humans. Of these, the most important ones are particles, carbon monoxide, nitrous oxide, sulfur oxides (coal), formaldehyde, and polycyclic organic hydrocarbons (*131,132*). But there are other substances as well, as demonstrated by the case of China, where the combustion of coal and coal bricks is the primary source of gaseous fluoride (*133*). In many cases the levels of indoor contaminants may exceed those registered outdoors. For example, indoor concentrations of particles are usually measured at levels 2–20 times greater than those set by U.S. EPA guidelines. Time–activity patterns (more time spent indoors than outdoors) seem to suggest that the total global dose equivalent for indoor pollution could be an order of magnitude greater than that for ambient pollution (*132*). Furthermore, it is important to consider that the exposure during brief high-intensity emission episodes accounts for 31–61% of the total exposure of household members who participate in the cooking process, and up to 11% for those who do not (*134*).

The adverse health effects reported in the literature are consistent with this exposure scenario. It has been estimated that anywhere from 2.7 million to 2.8 million deaths can be attributed to indoor pollutants (*131*). Moreover, the greatest burden of mortality arises from exposures to indoor pollutants in rural areas of developing countries (*131*). Estimates of the global burden of disease suggest that indoor air pollution is responsible for just less than 4% of the disability-adjusted life years lost (*135*). Therefore, the effects of indoor pollution are comparable to those of recreational tobacco use and are exceeded only by the effects of malnutrition (16%), unsafe water and sanitation (9%), and unsafe sex (4%) (*131,135*).

Evidence indicates that indoor air pollution increases the risk of chronic obstructive pulmonary disease and of acute respiratory infections in childhood. A relationship has also been established between indoor air pollution and low birth weight, increased infant and perinatal mortality, pulmonary tuberculosis, nasopharyngeal and laryngeal cancers, and (regarding the use of coal) lung cancer (*131,132,136*). Special mention should be made regarding China, where more than 10 million people suffer from dental and skeletal fluorosis because of burning high-fluoride coal (*133,137–139*).

All this information shows that indoor air pollution is a problem involving chemical mixtures. However, in addition to the exposure to those chemicals already mentioned in this section, indoor exposure to dioxins and public health insecticides also deserves attention. The principal indoor source of dioxins is biomass combustion, whereas DDT and deltamethrin are public health insecticides that are sprayed indoors for the control of malaria. Furthermore, we cannot rule out that indoor combustion increases dioxins levels in homes sprayed with DDT.

Few large groups are more disadvantaged globally than poor rural women and their young children in developing countries. These women and children experience the bulk of global airborne exposures to many indoor pollutants (*132*).

In conclusion, ambient air pollution is indeed an important issue, but indoor air pollution is a matter that urgently requires more attention.

Conclusions

The following are some of the research needs for developing countries in relation to mixtures: *a*) There is a clear need for study of the interaction between fluoride and arsenic, as they may have some mechanisms of toxicity in common (*74,75*). In addition both elements affect neuropsychological functions in exposed children (*25,140–142*). *b*) Another mixture of concern is that involving pyrethroids and DDT or its metabolites, as evidenced by the fact that co-exposure to these insecticides has been shown to occur in malaria areas (*104*). *c*) Considering the interaction of pyrethroids and organophosphates in humans (*99*), the mixture of these substances also deserves careful consideration. In many developing nations these compounds are used as public health insecticides in the same geographical areas. *d*) Another important mixture is that of pesticides and metals in polluted sites, common in developing countries. For example, in Mexico, some agricultural areas are naturally contaminated with arsenic; therefore, an interaction between pesticides and arsenic might be expected in these areas. Interestingly, it has been reported that in rats, arsenic pretreatment increased the acute toxicity of parathion, an organophosphate very much used in Mexico (*143*). *e*) Finally, there is an imperative need to assess the exposure to mixtures, and not simply to DDT, arsenic, or any other one particular substance. The exposure to mixtures experienced by populations worldwide is clear and indisputable; therefore, it is vital to reflect this fact in the health assessments. Furthermore, as previously stated (*144*), improved global monitoring programs would allow for more consistent data on trends over time, detection of new xenobiotics, and identification of disproportionately exposed populations. In this regard, human milk may be a valuable matrix, as it has been used for the identification of individuals exposed to mixtures in developing countries (*144–146*).

In addition to chemical mixtures there is a further need in less developed countries to study the interaction between chemicals and other factors such as nutritional conditions (increased absorption of some metals, lower levels of free radical scavengers), alcoholism (added effects in liver enzymes activity), low education (added neuropsychological effects), parasites (some organisms may modify the detoxification capacity of the liver), smoking, and ethnicity (use of folk medicines).

To better illustrate these needs, we have chosen to use malnutrition and smoking behavior as examples. Regarding malnutrition, the World Bank has estimated that 150 million children younger than 5 years are still malnourished in developing countries (*130*). Furthermore, 576 million individuals are expected to have nutritional deficiencies by the year 2015 (*130*). The need to study toxicological effects of chemical mixtures in regard to malnutrition is therefore evident.

However, the interaction with smoking is also important. Tobacco use worldwide has reached the proportion of a global epidemic, with little sign of abatement. Each year tobacco causes about 3.5 million deaths throughout the world. This translates to nearly 10,000 deaths per day. On the basis of current trends, this will increase to 10 million annual deaths during the 2020s and 2030s, with 7 million of these deaths occurring in developing countries (*147*). According to WHO estimates, there are around 1.1 billion smokers in the world, or about one-third of the global population ages 15 and up. Of these, 800 million are in developing countries (*147*). The number of smokers is easily translated into environmental tobacco smoke (ETS), considered an indoor pollutant (*132*). Exposure to ETS causes a wide variety of adverse health effects in children, including lower respiratory tract infections such as pneumonia and bronchitis, coughing and wheezing, worsening of asthma, and middle ear disease (*148,149*). Children's exposure to ETS may also contribute to cardiovascular disease in adulthood and to neurobehavioral impairment (*149*). Furthermore, prolonged exposure to ETS increases the risks of lung cancer (*150,151*). It is important to consider that ETS is a complex mix of more than 4,000 compounds (*152*). This mix contains more than 40 known or suspected human carcinogens (*152*), and recently an interaction between ETS and other contaminants has been shown. ETS exposure enhances the sensitivity of animals to ozone-induced lung injury (*153*).

In conclusion, complex mixtures are a public health issue in developing countries, especially in sites in the vicinity of smelters, mines, waste disposal sites, agricultural areas, and even at home. Therefore, research is needed not only to perform health assessments but also to study the types of chemical mixtures specific to developing countries. Furthermore, these studies must consider such factors as smoking, nutritional conditions, and alcoholism because these factors may modify the toxicity of the contaminants.

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